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EXAMINER	
ANDERSON, JAMES D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

## *Office Action Summary*	**Application No.** 10/682,584	**Applicant(s)** TAS ET AL.
	Examiner JAMES D. ANDERSON	**Art Unit** 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _3_ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _06 August 2008_.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) _44_ is/are pending in the application.
  4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) _44_ is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
  Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 8/6/2008, are acknowledged and entered. Claims 2-12, 29, 30, and 33-43 have been cancelled by Applicant. Claim 44 is pending and under examination.

In light of the new rejections set forth below, the finality of the previous Office Action is **withdrawn**.

Response to Arguments

Any previous rejections and/or objections to claims 2-12, 29, 30, and 33-43 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Reasons for Reopening Prosecution

In the previous Office Action, claim 44 was objected to as being dependent on a rejected base claim but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. In the amendment filed 8/6/2008, Applicants amended claim 44 to include all of the limitations of claim 41, from which it depended.

However, upon further consideration, pending claim 44 is herein rejected as being obvious over Dudek *et al.* in view of Taipale *et al.* (both prior art of record). Dudek *et al.* explicitly teach that administration of cyclopamine *in vivo* inhibits medulloblastoma tumor growth and further teaches, suggests, and motivates one skilled in the art to administer cyclopamine to treat aberrant growth states (*i.e.*, tumors) resulting from hedgehog gain-of-function, ptc los-of-function, or smoothened gain-of-function. Taipale *et al.* teach that basal cell carcinomas, medulloblastoma, rhabdomyosarcoma, and other human tumors are associated with mutations that activate the proto-oncogene *Smoothened* (*SMO*) or that inactivate the tumor suppressor *Patched* (*PTCH*). Smoothened and Patched are further taught to mediate the cellular response to the Hedgehog (Hh) secreted protein signal, and oncogenic mutations affecting these proteins cause excessive activity of the Hh response pathway. The authors demonstrate that cyclopamine, which inhibits the Hh response, is a potential “mechanism-based” therapeutic agent for the treatment of these tumors.

Accordingly, the fact that Applicants have identified the mechanism of action of cyclopamine (*i.e.*, induction of apoptosis) in the treatment of basal cell carcinoma is not considered to be patentable over the cited prior art, which teaches, suggests, and motivates the use of cyclopamine for the treatment of tumors in which oncogenic mutations cause excessive activity of the Hh response pathway.

Further, with regard to recitation of “...determining that Hedgehog/Smoothened signaling is utilized for inhibition of apoptosis of the tumor cells...” as recited in claim 44, it is the position of the Examiner that the claimed “determining" step is non-functional descriptive material that does not require an actual diagnostic step. Meaning of “process” as used in 35 U.S.C. §101 is narrower than its ordinary meaning, since claim is not patent-eligible “process” if it claims laws of nature, natural phenomena, or abstract ideas; thus, claim drawn to fundamental principle or mental process is unpatentable. In re Bilski (88 USPQ2d 1385).

In the instant case, recitation of “...determining that Hedgehog/Smoothened signaling is utilized for inhibition of apoptosis of the tumor cells...” is descriptive of a natural phenomenon or abstract idea. Any cell that has active Hedgehog/Smoothened signaling would necessarily use that signaling for inhibition of apoptosis, even if the prior art did not recognize of demonstrate that such is the case. In other words, it is not apparent from the claims and the specification that Applicants require any active measurement in order to actively demonstrate that Hedgehog/Smoothened signaling is utilized for inhibition of apoptosis of the tumor cells. For example, no such methods of determining whether Hedgehog/Smoothened signaling is utilized for inhibition of apoptosis of tumor cells are described in the specification. The fact that Applicants applied cyclopamine to a tumor and observed that apoptosis of tumor cells occurred is thus not patentable over prior art which teaches, suggests, and motivates the use of cyclopamine to treat tumors, despite the fact that the prior art did not recognize or observe that such use results in the apoptosis of tumor cells.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dudek et al. (USP No. 6,291,516; Issued Sep. 18, 2001; Filed Oct. 14, 1999) in view of Taipale et al. (Nature, August 2000, vol. 406, pages 1005-1009).

Dudek et al. teach methods of inhibiting aberrant growth states resulting from *hedgehog* gain-of-function, ptc los-of-function, or smoothened gain-of-function (Abstract). With regard to hedgehog gain-of-function, the inventors teach that this term refers to an aberrant modification or mutation of the ptc gene, hedgehog gene, or smoothened gene, which results in a phenotype which resembles contacting a cell with a hedgehog protein (e.g., exhibiting excess proliferation). For example, a tumor cell with an abnormally high proliferation rate due to activation of the hedgehog signaling pathway would have a "hedgehog gain-of-function" phenotype (col. 18, lines 46-67). As such, Dudek et al. implicitly suggest the determination of Hedgehog/Smoothened signaling in tumor cells in order to verify that a tumor has the "hedgehog gain-of-function" phenotype.

Suitable agents for use in the invention include cyclopamine as recited in the instant claim (Fig. 1; Fig. 3).

In one embodiment of the invention, the subject method can be used for the treatment of malignant medulloblastoma and other primary CNS malignant neuroectodermal tumors (col. 15, lines 52-57; col. 41, line 66 to col. 42, line 31). Figure 3 of Dudek et al. demonstrates that administration of cyclopamine to a mouse bearing a medulloblastoma tumor results in inhibition of tumor growth, thus meeting the limitation "cause a decrease of size" of the tumor as recited in instant claim 44.

The inventors also suggest that other tumors may, based on evidence such as involvement of the hedgehog pathway in these tumors, or detected expression of hedgehog or its receptor in these tissues during development, be affected by treatment with the subject compounds (col. 45, lines 12-28). The treatment of basal cell carcinomas based on the deregulation of hedgehog signaling pathway present in basal cell carcinomas cause by ptc mutations is also contemplated by Dudek et al. (col. 52, lines 13-17).

Taipale et al. teach that basal cell carcinomas, medulloblastoma, rhabdomyosarcoma, and other human tumors are associated with mutations that activate the proto-oncogene *Smoothened* (*SMO*) or that inactivate the tumor suppressor *Patched* (*PTCH*). Smoothened and Patched are further taught to mediate the cellular response to the Hedgehog (Hh) secreted protein signal, and oncogenic mutations affecting these proteins cause excessive activity of the Hh response pathway. The authors demonstrate that cyclopamine, which inhibits the Hh response, is a potential "mechanism-based" therapeutic agent for the treatment of these tumors (Abstract). In this regard, the authors note that loss-of-function mutations in PTCH or activating mutations in SMO are found in around 40% of sporadic basal cell carcinoma and 25% of primitive neuroectodermal tumors (page 1008, left column). The results shown in Taipale et al. indicate that cyclopamine inhibits the Shh pathway by antagonizing Smo and that the activation of the Hh response pathway by either type of oncogenic mutation is blocked by cyclopamine (id.).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer cyclopamine to patients having tumors resulting from *hedgehog* gain-of-function, ptc los-of-function, or smoothened gain-of-function as suggested and motivated by the cited prior art. The skilled artisan would have been imbued with at least a reasonable expectation of success given the fact that Dudek et al. demonstrate that administration of cyclopamine was effective in inhibiting the growth of medulloblastoma tumors *in vivo*. While the cited prior art does not explicitly teach or observe that cyclopamine induces apoptosis of tumor cells or that Hedgehog/Smoothened signaling is "utilized for the inhibition of apoptosis of the tumor cells" as recited in the instant claims, the recognition of the mechanism of action of the treatment methods suggested by the prior art is not considered to be a patentable distinction over the prior art because the cited references teach, suggest, and motivate one skilled in the art to administer cyclopamine to patients having tumors resulting from *hedgehog* gain-of-function, ptc los-of-function, or smoothened gain-of-function. As such, the fact that such administration, in addition to inhibiting tumor growth as demonstrated by Dudek et al., also can induce apoptosis of tumor cells, is not seen as a distinguishing feature of the instantly claimed methods.

Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Beachy et al. (USP No. 7,291,626; Issued Nov. 6, 2007; Filed Nov. 8, 2000) in view of Taipale et al. (Nature, August 2000, vol. 406, pages 1005-1009).

Beachy et al. teach methods of inhibiting smoothened-dependent pathway activation to counteract the phenotypic effects of unwanted activation of the hedgehog pathway, such as resulting from hedgehog gain-of-function, ptc loss-of-function, or smoothened gain-of-function (col. 6, lines 26-32). Such methods can be used to regulate proliferation and/or differentiation of cells in vitro and/or in vivo, e.g., to prevent the growth of hyperproliferative cells (col. 6, lines 45-50) or to treat conditions involving unwanted cellular proliferation (e.g., cancer and/or tumors such as medulloblastoma and basal cell carcinomas) (col. 2, lines 51-56; col. 10, lines 58-63 and lines 64-67; col. 46, lines 19-58). With regard to treatment methods, the inventors define an “effective amount” of a compound of the invention to mean an amount that brings about a change in the rate of cell proliferation and/or the state of differentiation of a cell and/or rate of survival of a cell (col. 12, lines 22-29). The compounds of the invention can be administered orally, parenterally, topically, or rectally (col. 47, lines 57-58) in doses ranging from 0.0001 to 100 mg/kg of body weight per day (col. 48, lines 54-61). The claims of the '626 patent specifically recite topical administration (claim 5), the treatment of basal cell carcinoma (claim 14) or medulloblastoma (claim 15), and administration of cyclopamine (claim 16).

Taipale et al. teach that basal cell carcinomas, medulloblastoma, rhabdomyosarcoma, and other human tumors are associated with mutations that activate the proto-oncogene *Smoothened* (*SMO*) or that inactivate the tumor suppressor *Patched* (*PTCH*). Smoothened and Patched are further taught to mediate the cellular response to the Hedgehog (Hh) secreted protein signal, and oncogenic mutations affecting these proteins cause excessive activity of the Hh response pathway. The authors demonstrate that cyclopamine, which inhibits the Hh response, is a potential “mechanism-based” therapeutic agent for the treatment of these tumors (Abstract). In this regard, the authors note that loss-of-function mutations in PTCH or activating mutations in SMO are found in around 40% of sporadic basal cell carcinoma and 25% of primitive neuroectodermal tumors (page 1008, left column). The results shown in Taipale et al. indicate that cyclopamine inhibits the Shh pathway by antagonizing Smo and that the activation of the Hh response pathway by either type of oncogenic mutation is blocked by cyclopamine (id.).

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to administer cyclopamine to patients having tumors resulting from *hedgehog* gain-of-function, ptc los-of-function, or smoothened gain-of-function as suggested and motivated by the cited prior art. The skilled artisan would have been imbued with at least a reasonable expectation of success given the fact that Taipale et al. clearly teach taht basal cell carcinomas, medulloblastoma, rhabdomyosarcoma, and other human tumors are associated with mutations that activate the proto-oncogene *Smoothened* (*SMO*) or that inactivate the tumor suppressor *Patched* (*PTCH*) and Beachy et al. teach that cyclopamine is useful in the treatment of these tumors. While the cited prior art does not explicitly teach that cyclopamine induces apoptosis of tumor cells or that Hedgehog/Smoothened signaling is "utilized for the inhibition of apoptosis of the tumor cells" as recited in the instant claims, the recognition of the mechanism of action of the treatment methods suggested by the prior art is not considered to be a patentable distinction over the prior art because the cited references teach, suggest, and motivate one skilled in the art to administer cyclopamine to patients having tumors resulting from *hedgehog* gain-of-function, ptc los-of-function, or smoothened gain-of-function. As such, the fact that such administration, in addition to inhibiting tumor growth as suggested by Beachy et al. and Taipale et al., also can induce apoptosis of tumor cells, is not seen as a distinguishing feature of the instantly claimed methods.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614